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(54) Zinc-containing compositions for oral administration including a copper compound and an aminoacid

(57) Compositions for oral use containing a zinc compound, a copper compound, an amino acid and a base material are described. The compositions provide for slow release of zinc ions upon dissolution in the mouth to thereby achieve beneficial therapeutic effects from the zinc ions. The copper compound provides copper ions which serve to counterbalance a large intake of zinc as is present upon prolonged oral use of the composition. A molar ratio of amino acid to zinc of 2 to 20 and a molecular ratio of copper to zinc of 0.1 to 0.01 provides compositions with a palatable taste and no aftertaste even upon the inclusion of the copper compound.

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Description

This invention relates to zinc compositions for oral use. More particularly, this invention relates to compositions containing a zinc compound and a relatively lesser amount of a copper compound which, when taken orally, is palatable and without undesirable aftertaste. These compositions include, in addition to the zinc compound and copper compound, a base material and an amino acid.

The value of nutritional supplements of elemental zinc is well established. Although zinc has been known to be essential for plant growth for more than a century, its essentiality for the normal growth of animals was reported in 1934 and for man in 1963. Hypogonadism in males, skin changes, poor appetite and mental lethargy are but some of the observable effects related to zinc deficiency in man. Carbonic anhydrase was the first metalloenzyme discovered in the 1930s. Today, approximately 100 enzymes, many of them essential to human well-being, have been found to contain zinc, and the evidence is strong that zinc is required for many (if not all) of these enzymes to express their activity. Several enzymes required for nucleic acid metabolism have been shown to require zinc. In this group are ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) polymerases, deoxythymidine kinase, and reverse transcriptase. It has been shown experimentally that the activity of deoxythymidine kinase in rapidly regenerating connective tissue decreases as early as six days after animals are placed on a zinc-deficient diet. This metabolic defect resulting from nutritional zinc deficiency is an indication of the fundamental importance of zinc for cell division and protein synthesis.

Until recently, zinc deficiency in man was considered unlikely because of the widespread availability of zinc in nature. However, recent evidence suggests that nutritional zinc deficiency may be common among the people of many developing countries where they subsist on high cereal protein diets. Only recently has it been recognised that the phytate content of such diets severely restricts zinc availability, which translates nutritionally to markedly depressed zinc absorption in man under many practical circumstances. Marginal zinc deficiency may be widespread even in the United States because of self-imposed dietary restrictions, use of alcohol and cereal proteins and the increasing use of refined foods which decrease the intake of trace elements. As meat is a major dietary source of zinc, vegetarians who consume cereals as a major source of protein may be in double jeopardy of zinc deficiency.

Therapeutically, zinc has a vital role in certain diseased or debilitated states. Zinc therapy is life-saving in acrodermatitis enteropathica, a genetic disease caused by an autosomal recessive trait which, although rare, had an extremely high mortality rate until it was discovered in 1973 that chronic administration of oral zinc salts was not only life-saving, but capable of lifetime control of the disease. Zinc supplementation markedly improves wound healing in zinc-deficient individuals. Zinc deficiency is an important feature in many cases of sickle cell anaemia characterised by growth retardation and hypogonadism, and zinc appears to have a pharmacological anti-sickling effect. Zinc has also been shown to be beneficial in the relief of acute inflammatory conditions associated with rheumatoid arthritis.

The safety of zinc supplements in excess of the amounts found in a normal diet is well documented. Although excessive zinc produces toxic symptoms, such symptoms are rare. An acute dose of 2 g of zinc sulphate has been recommended as an emetic. Except for extremely large doses, zinc is non-toxic. Nevertheless, it has been established that the chronic ingestion of zinc in daily amounts in excess of about 100 mg, i.e. about seven times the recommended daily allowance (RDA) of zinc as a nutritional supplement can, in some individuals, result in the depression of blood levels of the beneficial form of circulating lipoprotein known as high-density lipoprotein (HDL). It is further known that the biochemical mechanism that is responsible for this effect is the competitive inhibition of the absorption of cupric ion, Cu^{2+}, from the gut by the presence therein of greater-than-normal amounts of zinc ion, Zn^{2+}. Both ions rely upon the intermediacy of the metallothionine protein for transport across the gut wall into the bloodstream. Although cupric ions interact more strongly with metallothionine than do zinc ions, the presence of a relatively large amount of zinc ions can suppress the absorption of cupric ions by direct competition for the available metallothionine. The ultimate effect of this competitive inhibition of the absorption of copper is the undesirable depression of circulating HDL because the cupric ion is an essential component of one of the enzymes in the series that synthesises HDL in the body. It is further known that the inhibition of Cu^{2+} absorption from the gut by Zn^{2+} can be overcome if the individual who is ingesting the relatively large amounts of Zn^{2+} co-ingests about one to two RDAs of Cu^{2+}. The RDA for copper is 2 milligrams. A modest increase in copper intake is effective because of the aforementioned greater affinity of cupric ion for metallothionine, relative to the affinity of zinc ion for metallothionine.

Until the present time, the more or less water-soluble zinc compounds such as the sulphate, chloride, acetate, gluconate and the like have been formulated as solid tablets or enclosed in gelatin capsules which are swallowed whole. Accordingly, the taste buds and other taste apparatus in the mouth and throat are not affected. These formulations generally dissolve in the gastric juice of the stomach and release zinc ions to be absorbed into the system via the stomach and intestines. It was found by a serendipitous observation of G A Eby, D R Davis and W W Halcomb as reported in "Reduction in Duration of Common Colds by Zinc Gluconate Lozenges in a Double-Blind Study", Antimicrobial Agents and Chemotherapy, 25(1), pp 20-24 (1984) that when

modest quantities of zinc are slowly ingested by mouth so that the interior surfaces of the mouth and throat are intermittently bathed in a solution of ionic zinc, both the time course and the severity of the symptoms of the common cold are remarkably altered in a favourable way. Their double blind clinical study in 65 humans showed that allowing a tablet containing about 23 mg of elemental zinc, such as zinc gluconate, to slowly dissolve in the mouth once every two hours during 12 to 16 hours a day (the waking hours) reduced the duration of colds from 10.8 days in the untreated group to 3.9 days in the zinc-treated group; and at every time after about one day, the zinc-treated patients had a great reduction in cold symptoms compared to the patients who did not receive zinc. While the reported observations are highly significant, both from the point of view of statistical validity and of the importance of these observations to public health, the authors stated repeatedly in their paper that the disagreeable taste of the zinc gluconate tablets was a serious problem. Many patients receiving zinc gluconate discontinued the treatment on the first day "due to objection to the treatment". The authors stated that "the zinc gluconate lozenges [tablets] we used caused an unexpected unpalatability and distortion of taste in many subjects...." and mentioned "the somewhat bitter aftertaste which some people report for zinc gluconate." Furthermore, "unpalatable taste", "distortion of taste" and "mouth irritation" were common objections.

The original observation of the efficacy of unflavoured zinc gluconate tablets has received strong confirmation. Two large, double-blind, placebo-controlled clinical studies have been carried out and reported in the medical literature. The first was carried out at the Dartmouth College Cold Clinic in New Hampshire and reported by J C Godfrey, B Conant Sloane, D S Smith, J H Turco, N Mercer and N J Godfrey in "Zinc gluconate and the common cold: A controlled clinical study", Journal of International Medical Research, 20(2), pp 234-246 (1992). This study used sugar-based lozenges containing zinc gluconate equivalent to 23 mg of zinc and glycine prepared by serial dilution technology to produce a formulation according to US-A-4 684 528 and US-A-4 758 439. Participants in this study who met protocol requirements and who received active lozenges within two calendar days of the onset of cold symptoms and dissolved them in their mouths every 2 hours while awake, as specified in the protocol carried out under a US Investigational New Drug Application, experienced colds that lasted only 58% (mean duration) as long as patients who received a placebo. Patients in this study who received the active medication also experienced significant reductions of symptom severity and duration as compared to those who received the placebo.

The second double-blind study was done at the Cleveland Clinic Foundation by S B Moussad, M L Macknin, S V Medendork and P Mason and reported in "Zinc gluconate lozenges for treating the common cold", Annals of Internal Medicine, 125(2), pp 81-88 (1996). Patients who qualified for this study had cold symptoms for no more than 24 hours prior to entry. The study used zinc gluconate lozenges containing glycine, prepared in the same manner as for the Dartmouth study, but containing just 13.3 mg of zinc. When the data from this study were analysed on the same statistical basis as the Dartmouth study, i.e. using only the 83 out of 100 patients who met all criteria specified in the protocol, it was found that patients who took active medication had colds for only 52% as long as those who got a placebo. As in the Dartmouth study, patients in this study also experienced a rapid reduction in symptom severity, compared to those on a placebo.

As noted, zinc gluconate by itself has a very bad taste which may be overcome by formulations containing an excess of glycine or certain other selected amino acids such as described in US-A-4 684 528 and US-A-4 758 439. It has been found that nutritionally useful copper salts such as cupric gluconate, cupric sulphate, cupric acetate and cupric chloride also have undesirable organoleptic properties by themselves or in admixture with zinc gluconate in proportions (e.g. 1/33 mole of cupric salt per mole of zinc salt) that are useful to prevent the aforementioned adverse effect on HDLs.

Accordingly, in order to take advantage of the important effect of zinc upon the common cold while negating any potential adverse effect of zinc ingestion upon the high density lipoproteins of human beings, it is necessary to develop a formulation or formulations of pharmaceutically acceptable zinc salts combined with a minor proportion of cupric salts which are palatable enough to be taken with the frequency necessary to suppress symptoms of the common cold.

Another reason for developing zinc formulations having acceptable taste is to permit an increased or prolonged oral dosage. As described above, it has been found that the ingestion of zinc as tablets or capsules which pass directly to the stomach before disintegrating is ineffective for providing a zinc supplement for certain applications, including the control of cold symptoms. When zinc-containing lozenges are dissolved orally for treating an average common cold, no effect has been shown to occur on HDLs. However, if a user decides to take the zinc-containing lozenges on a daily basis as a dietary supplement or to control respiratory allergies, or has numerous colds occurring close in time, such prolonged intake of zinc can affect HDLs.

Accordingly, the problem underlying the invention is to provide a zinc supplement for oral usage which is palatable, which does not have a disagreeable aftertaste, and which permits a large oral dosage of zinc to be administered in simple and convenient form, without adversely affecting HDLs.

According to the present invention, there is provided a zinc-containing composition for oral use comprising a base material such as a candy or syrup, a zinc compound, and at least one amino acid and characterised

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by additionally including a minor molecular proportion of a copper compound, the molar ratio of amino acid to zinc being in the range of 2 to 20 and the molecular ratio of copper compound to zinc being in the range of 0.1 to 0.01. Such compositions may be formulated to be very pleasant to the taste and to leave no undesirable after-taste.

Amino acids which may be used in the compositions according to the invention are glycine, L-alanine, D,L-alanine, L-2-aminobutyric acid, D,L-2-aminobutyric acid, L-valine, D,L-valine, L-isovaline, D,L-isovaline, L-leucine, D,L-leucine, D-isoleucine, D,L-isoleucine, L-lysine and D,L-lysine. It has also been found that complexes between zinc and the named amino acids having the composition zinc(amino acid)$_2$ are water-soluble and have very good flavours when formulated with an excess of the same amino acid, excess being in the range of 2 to 20 moles of the amino acid per mole of zinc(amino acid)2. It has further been found that certain other amino acids, such as aspartic and glutamic acids, are not useful for this purpose. Therefore, it has been found that it is not possible to predict which zinc and amino acid combination will have an acceptable taste unless it is prepared and tested.

The zinc compound which can be used in combination with the amino acids noted above can be in any of the forms commonly used, such as the sulphate, chloride, acetate, gluconate, ascorbate, citrate, aspartate, picolinate, orotate and transferrin salts, as well as zinc oxide and complexes of divalent zinc with the amino acids. The minor proportion of the copper compound which can be used in combination with the zinc and amino acids noted above can be in any of the forms commonly used such as the sulphate, chloride, acetate, gluconate, ascorbate, citrate, aspartate, picolinate, orotate and transferrin salts as well as cupric oxide and complexes of divalent copper with the amino acids. It has been found, however, because of compatibility with the amino acids and the like, that the gluconate, citrate and acetate salts of zinc and copper are preferred.

The base material which can be used as a carrier for the zinc compound containing a minor molecular proportion of a copper supplement and the selected amino acid can be a sweetening agent such as a soft or hard candy base; a syrup such as corn syrup; a gum material including chewing gums; or any other form which permits the oral intake of the zinc compound and particularly where the composition is retained in the mouth for a substantial period of time to permit prolonged contact in the mouth with the zinc to provide a slow release of zinc into the mouth. Preferably the base material is a hard or soft candy base optionally containing a flavouring agent such as a fruit flavour concentrate or a syrup such as a natural or artificially sweetened syrup.

The zinc supplement compositions obtained according to the present invention which include the select amino acids and a trace of select copper salts to provide a proper balance in humans using this supplement in general possess very pleasant flavours. Although the characteristic flavour and mouth-feel of the zinc ion is present, it is markedly and unexpectedly modified by the presence of select amino acids and is not degraded by the presence of trace copper salts, to the extent that the unpalatable taste, distortion of taste, and mouth irritation associated with, for example, unformulated zinc gluconate, are greatly reduced or eliminated. This permits the formulation of compositions which will release over an extended period of time substantial amounts of zinc ions locally in the mouth and throat as necessary for certain applications, including control of the common cold. For example, a lozenge having a hard candy base will release approximately 14 mg of zinc ion uniformly over about 20 minutes in an adult human having a normal amount of saliva produced under the stimulation of hard candy. As will be apparent, the amount of zinc ion which will be released can be controlled by the amount of zinc compound incorporated into the base material.

The invention is illustrated by following examples of presently preferred compositions.

Examples 1 to 7 use hard candy stock as a base, while Example 8 uses a chewing gum base.

The preparation of the hard candy stock for use in Examples 1 to 7 is as follows:

A mixture of 400 g of sucrose, 160 ml of white corn syrup and 160 ml of deionised water was heated to 100°C while stirring in a one litre Teflon-lined aluminium pan. When a clear solution was obtained, the mixture was heated without further stirring at the maximum rate possible without boil-over until the temperature of the mixture reached 149°C. The pale straw-coloured product was poured in a 4 mm layer on to a lightly greased heavy aluminium pan. On cooling to room temperature, the layer was fractured into convenient-sized pieces and stored in a sealed container. The yield was 522.9 g of product known in the art as "hard crack" caramel.

Examples 1 to 7 illustrate hard candy bases containing from 2.31 to 4.67 mg of ionic zinc per gram of the composition and from 0.063 mg of cupric ion per gram of the composition.

EXAMPLE 1

Lemon-Flavoured Zinc Gluconate Formulation

70 grams of hard candy stock was placed in a stainless steel (SS) pan and heated while stirring to just thoroughly melt the stock. To this hot stock was added 5.510 g of a dry, finely-ground mixture containing 2.480 g of zinc gluconate trihydrate, 2.920 g of anhydrous glycine and 0.110 g of cupric gluconate. The dry compound was evenly distributed in the melted stock by thorough mixing and, while the resulting mixture was still hot, 1.0 ml of natural lemon flavour concentrate was added and stirred in. The still-hot mixture was distributed among 24 lightly greased steel candy moulds. The yield was 24 circular lozenges, average weight 2.6 g. The zinc con-

tent was 4.2 mg per gram and the copper content was 0 20 mg per gram

A similar product containing no glycine had an unpleasant flavour and aftertaste.

EXAMPLE 2

Lemon-Flavoured Zinc Acetate Formulation

70 grams of hard candy stock was placed in a stainless-steel (SS) pan and heated while stirring to just thoroughly melt the stock. To this hot stock was added 3.468 g of a dry, finely-ground mixture containing 0.780 g of zinc acetate dihydrate, 2.668 g of anhydrous glycine and 0.020 g of cupric acetate monohydrate. The dry compound was evenly distributed in the melted stock by thorough mixing and, while the resulting mixture was still hot, 1.0 ml of natural lemon flavour concentrate was added and stirred in. The still-hot mixture was distributed among 24 lightly greased steel candy moulds. The yield was 24 circular lozenges, average weight 2.6 g. The zinc content was 4.2 mg per gram and the copper content was 0.20 mg per gram.

A similar product containing no glycine had an unpleasant flavour and aftertaste.

EXAMPLE 3

Lemon-Flavoured Zinc Citrate Formulation

20.000 grams of hard candy stock was placed in a stainless steel (SS) pan and heated while stirring to just thoroughly melt the stock. To this hot stock was added 0.727 g of a dry, finely-ground mixture containing 0.200 g of zinc citrate dihydrate, 0.517 g of anhydrous glycine and 0.010 g of cupric citrate hemihydrate. The dry compound was evenly distributed in the melted stock by thorough mixing and, while the resulting mixture was still hot, 0.25 ml of natural lemon flavour concentrate was added and stirred in. The still-hot mixture was distributed among 24 lightly greased steel candy moulds. The final mixture was cooled in the pan and fractured into convenient-sized chunks for evaluation. The zinc content was 3.1 mg per gram and the copper content was 0.095 mg per gram.

A similar product containing no glycine had a sharp, unpleasant flavour and aftertaste.

EXAMPLE 4

Lemon-Flavoured Zinc Glycine Complex Formulations

(a) Preparation of Zinc Glycine Complex

A mixture of 4.0690 g, 0.500 mole of ultra-pure zinc oxide (ZnO) and 8.2577 g, 0.1100 mole of anhydrous glycine was heated to 88°C in 75 ml of deionised water for 30 minutes in a boiling water bath. Only a small amount of white substance remained insoluble. The solution was gravity-filtered while hot the filter was washed with 5 ml of hot water, and the filtrate was chilled in an ice bath. The resulting crystalline precipitate was filtered off, washed with 60 ml of 91% isopropyl alcohol, and air dried for 12 hours at 65.5°C. The yield was 6.805 g.

Analysis calculated for zinc glycinate sesquihydrate: ZnO, 33.83%.

Analysis found: ZnO, 33.51%.

The complex between zinc and glycine is a known compound as described in "Glycinate Complexes of Zinc and Cadmium", B W Low, F K Hirshfield and F M Richards, J Am Chem Soc, 81, 4412-4416 (1959); J V Dubsky and A Rabas, Spisy Vidavny Prevodovedecisou Fakultou Masarykovy Univ., No 123, 3-18 (1930); Chem Abstr 25, 26557 (1932); and "Complex Formation Between Metallic Cations and Proteins, Peptides and Amino Acids", F R N Gurd and P F Wilcox, Adv in Protein Chem., 11, 311-348 (1956).

(b) Lemon-Flavoured Product Preparation

22.500 grams of hard candy stock was placed in a stainless steel (SS) pan and heated while stirring to just thoroughly melt the stock. To this hot stock was added 0.792 g of a dry, finely-ground mixture containing 0.400 g of zinc glycinate sesquihydrate, 0.3750 g of anhydrous glycine and 0.0166 g of cupric sulphate pentahydrate. The dry compound was evenly distributed in the melted stock by thorough mixing and while the resulting mixture was still hot, 0.25 ml of natural lemon flavour concentrate was added and stirred in. The mixture was cooled in the pan and then fractured into convenient-sized chunks. The zinc content was 4.67 mg per gram and the copper content was 0.182 mg per gram.

A similar product containing no glycine had an unpleasant flavour and aftertaste.

EXAMPLE 5

Lemon-Flavoured Zinc Alanine Complex Formulations

(a) Preparation of Zinc-Alanine Complex

A mixture of 4.0690 g, 0.500 mole of ultra-pure zinc oxide (ZnO) and 8.909 g, 0.1000 mole of anhydrous D,L-alanine was heated to 88°C in 75 ml of deionised water for 20 minutes in a boiling water bath. An appreciable amount of substance remained insoluble. The solution was gravity-filtered while hot and the clear filtrate was diluted to a total volume of 170 ml with 91% isopropyl alcohol. On cooling to -4°C, a crystalline product formed. The crystalline precipitate was filtered off and air dried for 12 hours at 65.5°C. The yield was 4.897 g.

Analysis calculated for zinc D,L-alaninate hemihydrate: ZnO, 32.48%.

Analysis found: ZnO 32.60%.

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The complex between zinc and D,L-alanine is a known compound as described in "Chemotherapeutic Drugs Against Viruses. XXXIV. Antiviral Effects of Zinc Complexes on Japanese B Encephalitis Virus", S Akihama and S Toyoshima, Chem Pharm Bull (Tokyo), 10, 1254-1257 (1962); and "Chelation of some Bivalent Metal Ions with Alanine and Phenylalanine", V Simeon and A O Weber, Croat Chem Acta, 38, 161-167 (1966).

(b) Lemon-Flavoured Product Preparation

20.500 grams of hard candy stock was placed in a stainless steel (SS) pan and heated while stirring to just thoroughly melt the stock. To this hot stock was added 0.1355 g of a dry, finely-ground mixture containing 0.1350 g of zinc D,L-alaninate hemihydrate, 0.3750 g of anhydrous glycine and 0.0055 g of cupric phosphate trihydrate. The dry compound was evenly distributed in the melted stock by thorough mixing and while the resulting mixture was still hot, 0.25 ml of natural lemon flavour concentrate was added and stirred in. The mixture was cooled in the pan and then fractured into convenient-sized chunks. The zinc content was 2.31 mg per gram and the copper content was 0.116 mg per gram.

A similar product containing no glycine had an unpleasant flavour and aftertaste.

(c) Preparation of Product with Added Alanine

The same procedure was used to combine 21.600 g of hard candy stock, 0.1500 g of zinc D,L-alaninate hemihydrate, 0.0067 g of cupric tartrate trihydrate and 0.5000 g of D,L-alanine. The resulting product contained 2.47 mg of zinc per gram and 0.072 mg of copper per gram. It had a pleasant taste, with no unpleasant aftertaste.

EXAMPLE 6

Lemon-Flavoured Zinc L-leucine Formulations

(a) Preparation of Zinc L-leucine Complex

Anhydrous L-leucine, 5.2472 g, 0.0400 mole was dissolved in 30 ml of deionised water and heated to 49°C. Ultra-pure zinc acetate dihydrate 4.3900 g, 0.200 mole was added in small increments over one hour, with stirring. The solution did not clear, so another 20 ml of water was added and the mixture was heated in a boiling water bath to 88°C for an additional 2½ hours. Water was then added to a total volume of 75 ml, the mixture was heated again to 88°C and gravity-filtered.

The retained solid was dried at 65.5°C for 12 hours, found to weigh 2.717 g, and was analysed.

Analysis calculated for zinc L-leucinate monohydrate: ZnO 24.98%.

Analysis found: ZnO, 25.46%.

The clear filtrate from this first product was diluted to 300 ml with 91% isopropyl alcohol. The resulting precipitate of white flakes was filtered off and dried. Before drying, a few of the flakes were found to be immediately soluble in a few drops of water. After drying for 12 hours at 65.5°C the product, 1.1216 g, was no longer freely soluble in water.

Analysis calculated for anhydrous zinc L-leucinate: ZnO, 26.45%.

Analysis found: ZnO, 26.51%.

The complex between zinc and L-leucine is a known compound as described in "Chemotherapeutic Drugs Against Viruses. XXXIV Antiviral Effects of Zinc Complexes on Japanese B Encephalitis Virus", S Akihama and S Toyoshima, Chem Pharm Bull (Tokyo), 10, 1254-1257 (1962).

(b) Lemon-Flavoured Product Preparation

20.5000 grams of hard candy stock was placed in a stainless steel (SS) pan and heated while stirring, to just thoroughly melt the stock. To this hot stock was added 0.3005 g of a dry, finely-ground mixture containing 0.2930 g of anhydrous zinc L-leucinate and 0.0075 g of cupric glycinate dihydrate. The dry compound was evenly distributed in the melted stock by thorough mixing and while the resulting mixture was still hot, 0.25 ml of natural lemon flavour concentrate was added and stirred in. The mixture was cooled in the pan and then fractured into convenient-sized chunks. The zinc content was 2.82 mg per gram and the copper content was 0.092 mg per gram.

(c) Preparation of Product with Added Glycine

The same procedure was used to combine 21.6000 g of hard candy stock, 0.4170 g of anhydrous zinc L-leucinate, 1.3500 g of anhydrous glycine, and 0.0106 g of cupric glycinate dihydrate. The resulting product had a zinc content of 3.53 mg per gram and a copper content of 0.116 mg per gram.

EXAMPLE 7

Lemon-Flavoured Zinc D,L-Lysine Complex Formulations

(a) Preparation of Zinc D,L-lysine Complex

A mixture of 2.035 g, 0.025 mole of ultra-pure ZnO, 7.310 g, 0.050 mole of anhydrous D,L-lysine and 25 ml of deionised water was heated and stirred at 83°C for 20 minutes. The cloudy solution was gravity filtered and the filter was rinsed with another 20 ml of hot water. No indication of a precipitate appeared when the clear filtrate was cooled to 29.5°C, so 225 ml of 91% isopropyl alcohol was added. A layer of oil settled to the bottom of the beaker. On cooling at room temperature overnight, the oil crys-

tallised The white solid was filtered off and dried at 65 5°C for 21 hours Yield: 6 80 g.

Analysis calculated for zinc D,L-lysinate tetrahydrate: ZnO, 19.02%.

Analysis found: ZnO, 19.15%.

The complex of zinc with D,L-lysine is a known compound as described in "Chemotherapeutic Drugs Against Viruses. XXXIV. Antiviral Effects of Zinc Complexes on Japanese B Encephalitis Virus", S Akihama and S Toyoshima, Chem Pharm Bull. (Tokyo), 10, 1254-1257 (1962).

(b) Lemon-Flavoured Product Preparation

20.1000 grams of hard candy stock was placed in a stainless steel (SS) pan and heated while stirring to just thoroughly melt the stock. To this hot stock was added 0.459 g of a dry, finely-ground mixture containing 0.450 g of zinc D,L-lysinate tetrahydrate and 0.009 g of cupric salicylate tetrahydrate. The dry compound was evenly distributed in the melted stock by thorough mixing and while the resulting mixture was still hot, 0.25 ml of natural lemon flavour concentrate was added and stirred in. The mixture was cooled in the pan and then fractured into convenient-sized chunks. The zinc content was 3.35 mg per gram and the copper content was 0.068 mg per gram.

(c) Preparation of Product with Added Glycine

The same procedure was used to combine 20.1000 g of hard candy stock, 0.450 g of zinc, D,L-lysinate tetrahydrate, 1.180 g of anhydrous glycine, and 0.010 g of cupric salicylate tetrahydrate. The resulting product had a pleasant flavour and contained 3.16 mg of zinc and 0.071 mg of copper per gram.

Similar formulations having good to excellent palatability are prepared from the zinc complexes of D,L-alpha-aminobutyric acid, L-valine, D,L-valine, L-isoleucine, D,L-isoleucine, L-isovaline, D,L-isovaline, L-lysine and L-alanine. Similar formulations prepared with the dibasic amino acid/zinc complexes of L-aspartic acid, D,L-aspartic acid, L-glutamic acid and D,L-glutamic acid were found to be highly unpalatable and to leave undesirable and persistent aftertaste.

EXAMPLE 8

This example uses chewing gum as a base material in the preparation of a spearmint-flavoured chewing gum containing zinc gluconate, copper gluconate and glycine.

64.000 g of spearmint gum was heated in a pyrex bowl at 121°C for 20 minutes and 6.359 g of a finely-ground mixture of 2.750 g of zinc gluconate trihydrate, 4.050 g of anhydrous glycine and 0.0594 g of cupric gluconate monohydrate was blended into it with a stainless steel spoon. The mixture cooled rapidly, but its temperature was maintained by giving it two bursts of 750 Watt microwave energy totalling 35 seconds during the blending process. When it was thoroughly blended, the mixture was allowed to cool to about 40°C and rolled into a 3 mm sheet that was then cut up into sticks weighing 3.1 g. This product contained 4.98 mg of zinc and 0.11 mg of copper per gram. The flavour and consistency were excellent. Zinc is slowly released upon chewing, as shown by EDTA (ethylenediamine tetraacetic acid), titration of zinc ion in the saliva and by the typically astringent zinc mouth-feel, but the flavour remains pleasant and there is no unpleasant aftertaste.

Claims

1. A slow release composition for oral consumption comprising a base material uniformly containing a zinc compound and an amino acid, the zinc being slowly and uniformly released as the composition is orally consumed, characterised in that the composition further includes a copper compound, that the molar ratio of the amino acid to zinc is from 2 to 20 and that the copper compound is present in a molecular ratio to the zinc of 0.1 to 0.01.

2. A slow release composition according to Claim 1, characterised in that the amino acid is selected from a group consisting of glycine, L-alanine, D,L-alanine, L-2-amino-butyric acid; D,L-2-aminobutyric acid, L-valine, D,L-valine, L-isovaline, D,L-isovaline, L-leucine, D,L-leucine, D-isoleucine, D,L-isoleucine, L-lysine and D,L-lysine.

3. A slow release composition according to Claim 1 or 2, characterised in that the copper compound is selected from a group consisting of cupric L-alaninate, cupric carbonate, cupric chloride, cupric citrate, cupric gluconate, cupric glycinate, cupric oxide, cupric salicylate, cupric sulphate, and cupric tartrate.

4. A composition according to any one of claims 1 to 3 wherein the composition contains from 1 mg to 5 mg of zinc for each gram of the total composition.

5. A composition according to any one of claims 1 to 4 wherein the amino acid is glycine.

6. A composition according to any one of Claims 1 to 5 wherein the zinc compound is a zinc salt in the form of a sulphate, chloride, acetate, gluconate, ascorbate, citrate, aspartate, picolinate, orotate and transferrin salt.

7. A composition according to any one of Claims 1 to 5 wherein the zinc compound is a complex of divalent zinc with an amino acid

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8. A composition according to Claim 7 wherein the zinc complex is a zinc glycine complex having a formula $Zn(C_2H_4NO_2)$ 2.nH20 in which n has value of 1, 1.5 or 2, and the composition contains from 1.8 to 7.1 parts by weight of anhydrous glycine per part by weight of the zinc complex.

9. A composition according to Claim 7 wherein the zinc complex is a zinc alanine complex having a formula $Zn(C_3H_6NO_2)$ 2.n$H_2$0 in which n has a value of 0.5, 1 or 2, and the composition contains from 1.8 to 7.1 parts by weight of anhydrous alanine per part by weight of the zinc complex.

10. A composition according to Claim 7 wherein the zinc complex is a zinc D,L-lysine complex having a formula $Zn(C_6H_{13}\ N_2O_2)_2.4H_2O$ and the composition contains from 0.9 to 3.5 parts by weight of anhydrous glycine per part by weight of the zinc complex.

11. A composition according to Claim 7 wherein the zinc complex is a zinc L-leucine complex having a formula $Zn(C_6H_{12}\ NO_2)_2$ and the composition contains from 1.1 to 4.6 parts by weight of anhydrous glycine per part by weight of zinc complex.

12. A composition according to Claim 7 wherein the zinc complex is a zinc D,L-alpha-aminobutyric acid complex having a formula $Zn(C_4H_3NO_2)_2$, and the composition contains from 1.4 to 5.6 parts by weight of anhydrous glycine per part by weight of zinc complex.

13. A composition according to Claim 7 wherein the zinc complex is a zinc L-valine complex having a formula $Zn(C_5H_{10}NO_2)_2$, and the composition contains from 1.2 to 5.0 parts by weight of anhydrous glycine per part by weight of zinc complex.

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 97 30 9237

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	US 4 837 219 A (HUTTERER JEFFREY) * abstract * * column 4; claim 1 * ---	1-6	A61K33/30 A61K31/315 A61K31/30 A61K33/34 A61K31/195 //(A61K33/34, 33:30,31:195), (A61K33/34, 31:315, 31:195), (A61K33/30, 31:30,31:195), (A61K31/315, 31:30,31:195)
X	GB 2 022 998 A (BERES J) * examples 1-3; tables 1,4 * * claims 1,10,11,22,24,31 * ---	1-6	
X	FR 2 674 755 A (THOREL JEAN NOEL ;MOREAU PIERRE (FR)) * page 2, line 15 - page 4, line 5 * * page 4, line 25 - page 5, line 30 * * claim 9; examples 1,3,5 * ---	1-6	
Y	US 4 758 439 A (GODFREY JOHN C) * abstract * * the whole document * ---	1-13	
Y	US 5 075 116 A (LAHAYE PETER G ET AL) * column 5, paragraph 3 - column 6 * --- -/--	1-13	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 January 1998	Gonzalez Ramon, N

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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INCOMPLETE SEARCH
SHEET C

Application Number
EP 97 30 9237

Claim(s) searched completely:
0

Claim(s) searched incompletely:
1-13

Reason for the limitation of the search:

In view of the large number of compounds, which are defined by the general definition in the independent claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, examples and to the general idea underlying the application (see Guidelines, Part B, Chapter III, paragraph 3.6).

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 97 30 9237

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 116, no. 18, 4 May 1992 Columbus, Ohio, US; abstract no. 181171, ORBAN, GYULA ET AL: "Roborant oral composition comprising vitamins, amino acids and trace elements" XP002053245 * abstract * & HU 57 046 A (HUNG.)	1-13	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

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INCOMPLETE SEARCH
SHEET C

Application Number
EP 97 30 9237

Claim(s) searched completely:
0

Claim(s) searched incompletely:
1-13

Reason for the limitation of the search:

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